Behavioural Brain Research 257 (2013) 286–294

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Time-dependence of risperidone and asenapine sensitization and associated D_2 receptor mechanism

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HIGHLIGHTS

- Repeated risperidone and asenapine treatment enhanced acute effect of these drugs in the conditioned avoidance model.
- Risperidone and asenapine sensitization lasted up to 40 days.
- Risperidone and asenapine sensitization increased with the passage of time.
- Repeated risperidone treatment caused a functional upregulation of dopamine $D_{2/3}$ receptors.

ARTICLE INFO

Article history:
Received 20 August 2013
Received in revised form
23 September 2013
Accepted 27 September 2013
Available online 5 October 2013

Keywords:
Time-dependent sensitization (TDS),
Asenapine
Risperidone
Conditioned avoidance response
Quinpirole
Locomotor activity

ABSTRACT

When an antipsychotic drug is given repeatedly and intermittently, there is often a long-term increase in its behavioral efficacy, termed antipsychotic sensitization. With the passage of time, the magnitude of antipsychotic sensitization may increase or decrease based on the principle of time-dependent sensitization (TDS) or memory decay, respectively. In the present study, we examined the time-dependent feature and possible dopamine D_2 receptor mechanism of sensitization induced by risperidone and asenapine in the conditioned avoidance response test. Well-trained male adult Sprague-Dawley rats were first repeatedly treated with risperidone (1.0 mg/kg) or asenapine (0.2 mg/kg) and tested for avoidance response daily for 5 consecutive days. Eight, 18 or 38 days after the 5th drug treatment, all rats were retested drug-free to assess the long-term impact of prior risperidone or asenapine treatment. Drug-pretreated rats had significantly lower avoidance than vehicle-pretreated ones on this test, and the group differences increased with the passage of time. In the subsequent drug challenge test at 10, 20 or 40 days after the 5th drug treatment, all rats were injected with a low dose of risperidone (0.3 mg/kg) or asenapine (0.1 mg/kg). Drug-pretreated rats again made significantly fewer avoidances than controls, confirming the antipsychotic sensitization effect. Finally, in the quinpirole (a $D_{2/3}$ receptor agonist, 1.0 mg/kg, sc)-induced hyperlocomotion test, risperidone-pretreated rats exhibited a significantly higher level of motor activity than the vehicle-pretreated ones. These findings suggest that risperidone and asenapine sensitization is long-lasting, follows the TDS principle, and is likely mediated by D_2 receptor supersensitivity.

1. Introduction

It is well documented that repeated and intermittent administrations of most antipsychotic drugs often cause an increase in the behavioral responsiveness to these drugs. This phenomenon is termed antipsychotic sensitization. Supersensitivity psychosis, tardive dyskinesia, and time-dependent increase in antipsychotic response are several well-known clinical examples of antipsychotic sensitization [1–3]. In preclinical studies, antipsychotic sensitization has been demonstrated in several different behavioral models [4–7]. It is often measured using two methods [8] similar to those used for assessing psychostimulant-induced behavioral sensitization [9]. The first index of antipsychotic sensitization is revealed through a within-subjects comparison, in which the behavioral effect of a drug is stronger on the last treatment day than the first day (e.g. a comparison between days 1 and 5). The second index of antipsychotic sensitization is provided by a between-subjects comparison, in which the behavioral response of drug-pretreated animals to a challenge dose of an antipsychotic drug is compared to the response of vehicle-pretreated control animals. Here, antipsychotic sensitization is revealed by an increased sensitivity to the drug challenge in drug-pretreated animals relative to those pretreated with vehicle.

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http://dx.doi.org/10.1016/j.bbr.2013.09.050

The conditioned avoidance response (CAR) model is an aversively motivated instrumental conditioning task commonly used in the preclinical study of antipsychotic drugs (APDs) [10,11]. In this model, animals are trained to prevent the occurrence of an aversive stimulus (e.g., electric footshock) by performing a specific response to a conditioned stimulus (e.g., tone). Persistent avoidance response is thought to resemble a persecutory delusion [12]. Antipsychotic drugs selectively disrupt avoidance responding without altering unconditioned escape response [13,14], and this feature has been effectively used to identify potential antipsychotic drugs, to differentiate antipsychotic drugs from other classes of psychotropic drugs, and to predict the clinical potency of antipsychotic drugs [11,14,16–18]. Our recent work focuses on behavioral characteristics and neurobiological mechanisms of antipsychotic sensitization in the conditioned avoidance response (CAR) and phencyclidine (PCP)-induced hyperlocomotion models, two animal behavioral tests sensitive to antipsychotic activity [8,19–23]. We have shown that repeated administration of haloperidol, olanzapine, asenapine or risperidone daily for 5–7 days tends to cause a progressively increased inhibition of avoidance responding and PCP-induced hyperlocomotion over days (a within-subjects sign of sensitization). A few days later, when all rats are given a challenge dose of these drugs, they often make significantly *fewer* avoidance responses and exhibit *lower* PCP-induced hyperlocomotion than those that are treated with these drugs for the first time (a between-subjects sign of sensitization). In addition, repeated administration of haloperidol and olanzapine causes a sensitization effect that can last up to 17 days [8], and are likely mediated by dopamine D_2 and 5-HT_{2A} receptor-related neural plasticity [24]. Recently, we further show that olanzapine sensitization can be induced in adolescent rats and this effect can last up to 45 days and persist into adulthood [21].

Antipsychotic sensitization likely reflects a composite impact from two sources. One is the relatively specific pharmacological actions of a given antipsychotic drug. As mentioned before, this is likely mediated by a drug's actions on its immediate neuroreceptor targets (e.g., D_2 and 5-HT_{2A} receptors) [24] and should follow the basic principles of learning and memory, as antipsychotic sensitization represents a non-associative form of learning and memory. Under this principle, the magnitude of sensitization should decrease with the passage of time due to a memory trace decay process (similar to forgetting). Another source is the ubiquitous adaptive response to the foreign aspect of the drug (any drug is an exogenous agent to an organism), which tends to follow the "time-dependent sensitization (TDS)" principle. This principle, first articulated by Antelman and his colleague [25], suggests that a drug effect often grows (i.e., sensitized or strengthened) with the passage of time upon acute exposure to the drug. In Antelman's earlier work, he found that a single exposure to a clinically low dose of antipsychotic produced changes that were shown up to 8 weeks later [6]. In our previous study on the time course of antipsychotic sensitization [8], we assessed the magnitude of haloperidol and olanzapine sensitization in the conditioned avoidance response test at 4, 10, or 17 days after the last drug treatment. We did not find that haloperidol or olanzapine sensitization changed its magnitude over time, but maintained at a high level throughout the post-injection period. One limitation of the study was shorter time courses tested. It is possible that with a prolonged period of testing, the time-dependent feature of antipsychotic sensitization could be revealed.

The present study addressed this limitation by examining the potential time-dependent feature of antipsychotic sensitization induced by risperidone and asenapine, which represent the earliest and latest atypical antipsychotic drugs in a broader time frame. Both drugs are medically approved for the treatment of schizophrenia and bipolar disorders, with a multiple receptor binding profile targeting dopamine D_2 and D_1 receptors, serotonin receptors (5-HT_{2A}, 5-HT_{2C}, 5-HT_7), adrenergic α_1 and α_2 receptors, histamine H_1 and H_2 receptors, etc. [26,27]. Both drugs have shown to give rise to a sensitization effect in animal tests of antipsychotic activity, including conditioned avoidance test and PCP-induced hyperlocomotion. We also investigated the involvement of dopamine D_2 receptor as a biological mechanism underlying antipsychotic sensitization by comparing the quinpirole-induced increase in motor activity in drug-pretreated animals to vehicle-pretreated animals. Because quinpirole is a selective $D_{2/3}$ receptor agonist, a higher level of motor activity under quinpirole challenge presumably reflects an upregulation of D_2 receptor function [28,29]. Quinpirole-induced hyperlocomotion is also thought to be mediated through an increase in the efficacy of the post-synaptic $D_{2/3}$ transductional mechanisms [30,31], and has been widely used to assess drug or non-drug induced changes in $D_{2/3}$ functions [32,33].

2. Materials and methods

2.1. Animals

Adult male Sprague-Dawley rats (226–250 g upon arrival, Charles River, Portage, MI) were housed two per cage, in 48.3 cm × 26.7 cm × 20.3 cm transparent polycarbonate cages under 12-h light/dark conditions (light on between 6:30 am and 6:30 pm). Room temperature was maintained at 22 ± 1 °C with a relative humidity of 45–60%. Food and water was available ad libitum. Animals were allowed at least 5 days of habituation to the animal facility before being used in experiments. All behavioral tests took place between 9 am and 5 pm in the light cycle. All experimental treatment and procedures were approved by the Institutional Animal Care and Use Committee at the University of Nebraska-Lincoln.

2.2. Drugs and choice of doses

Risperidone (RIS) (a gift from the NIMH drug supply program) was dissolved in distilled sterile water with 1.0% glacial acetic acid. Asenapine maleate (ASE) (a gift from the NIMH drug supply program) and quinpirole hydrochloride (Tocris Bioscience, Bristol, UK) were dissolved in 0.9% saline. All drugs were administered subcutaneously in a volume of 1.0 ml/kg body weight. Doses of RIS (1.0 and 0.3 mg/kg, for drug test and challenge respectively) and ASE (0.2 and 0.1 mg/kg, for drug test and challenge respectively) were chosen on the basis of literature review showing that these doses produce a reliable disruption of avoidance responding and cause a sensitization effect [23,34–39]. The chosen quinpirole dose (1.0 mg/kg) targets post-synaptic D_2 receptors and causes an increase in motor activity [29,40–42].

2.3. Two-way avoidance conditioning apparatus

Ten identical two-way shuttle boxes custom designed and manufactured by Med Associates (St. Albans, VT) were used. Each box was housed in a ventilated, sound-insulated isolation cubicle (96.52 cm W × 35.56 cm D × 63.5 cm H). Each box was 64 cm long, 30 cm high (from grid floor), and 24 cm wide, and was divided into two equal-sized compartments by a partition with an arch style doorway (15 cm high × 9 cm wide at base). A barrier (4 cm high) was placed between the two compartments, so the rats had to jump from one compartment to the other. The grid floor consisted of 40 stainless-steel rods with a diameter of 0.48 cm, spaced 1.6 cm apart center to center, through which a scrambled footshock (as an unconditioned stimulus, US; 0.8 mA, maximum duration: 5 s) was delivered by a constant current shock generator (Model ENV-410B)